Effects of Treatment on Morbidity in Hypertension

III. Influence of Age, Diastolic Pressure, and Prior Cardiovascular Disease; Further Analysis of Side Effects

VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP ON ANTIHYPERTENSIVE AGENTS

SUMMARY

Additional data are presented from the Veterans Administration Cooperative Study with respect to the 194 control and 186 treated male patients with initial diastolic blood pressures averaging 90–114 mm Hg. Attack rates and effectiveness of treatment were examined with respect to the following risk factors present at entry: (1) cardiovascular-renal (CVR) abnormalities, the prevalence of which was higher than in the general population of hypertensive patients; (2) diastolic blood pressure; and (3) age. Both attack rates and effectiveness of treatment increased directly with the number of these risk factors present at entry. Age and presence of CVR abnormalities at entry appeared to strongly influence subsequent attack rates, whereas entry level of blood pressure had a relatively smaller effect on attack rates. On the other hand, "effectiveness of treatment" appeared to be most influenced by the initial level of blood pressure. Patients with prerandomization diastolic blood pressure in the range of 90 to 104 mm Hg derived relatively little benefit from treatment unless they had CVR abnormalities at entry or were over 50 years of age. A longer period of follow-up would be needed to assess the value of treatment in the lower risk subgroups.

With respect to side effects, the incidence of mild hypokalemia, hyperuricemia, and elevated fasting blood sugar was significantly higher in the treated group. These and other side effects should be weighed against the benefit to be expected from treating hypertensive patients at low risk.

From the Veterans Administration Hospital, Washington, D. C.

Permanent Members of the Study Group: Massimo Calabresi, M.D., C. Hilmon Castle, M.D., Leo Elson, M.D., Edward D. Freis, M.D. (Chairman), Rudolph E. Fremont, M.D., Michael A. Harris, M.D., David Littman, M.D., Eli A. Ramirez, M.D., and J.R. Thomas, M.D.

Other Members: Luis A. Arias, M.D., Mark L. Armstrong, M.D., Alston W. Blount, M.D., Thomas A. Bruce, M.D., Ovid B. Bush, Jr., M.D. (deceased), Eugene C. Clark, M.D., Annette Fitz, M.D., R. M. Freeman, M.D., Edward D. Frohlich, M.D., Arthur Gear, M.D., John D. Kyriacopoulos, M.D., Alan R. Lyon, M.D., Gloria D. Massaro, M.D., Donald McCaughan, M.D., Jean Morgan, M.D., Henry W. Overbeck, M.D., Eliseo C. Perez-Stable, M.D., Mitchell H. Perry, M.D., Roger Sutton, M.D., and James Taguchi, M.D.

Biostatisticians: Russell B. Tewksbury, Sc.D. (deceased), Paul D. Williams, M.S., and Lawrence Shaw, A.M.

Central Office Coordinator: Harold W. Schnaper, M.D.

Participating Veterans Administration Hospitals: Allen Park, Michigan, Birmingham, Alabama, Brooklyn, New York, Dayton, Ohio, Iowa City, Iowa, Jackson, Mississippi, Memphis, Tennessee, Nashville, Tennessee, Oklahoma City, Oklahoma, Pittsburgh, Pennsylvania, Richmond, Virginia, Salt Lake City, Utah, St. Louis, Missouri, San Juan, Puerto Rico, Washington, D. C., West Haven, Connecticut, and West Roxbury, Massachusetts.

Address for reprints: Dr. Edward D. Freis, Veterans Administration Hospital, 50 Irving Street, N.W., Washington, D.C. 20422.

Received September 28, 1971; revision accepted for publication December 21, 1971.

THE VETERANS Administration Cooperative Study Group previously reported on the results of a randomized, double-blind clinical trial in 194 control and 186 treated male patients with initial diastolic blood pressures averaging 90 through 114 mm Hg followed prospectively for periods up to 5.5 years, average 3.3 years.[1] Treatment consisted of a combination of hydrochlorothiazide, reserpine, and hydralazine. There were 19 deaths related to cardiovascular disease in the control group and eight in the treated series. Life table analysis indicated that the risk of a morbid event, fatal or nonfatal, over a 5-year period was reduced from 55 to 18% by treatment. Congestive heart failure, stroke, and progressive renal damage were sharply reduced or eliminated in the treated patients. However, the incidence of myocardial infarction and sudden death was essentially the same in the control and treated groups. In addition to assessable morbid events, 20 control patients versus none of the treated group developed persistent diastolic elevations of 125 mm Hg or higher.

In the initial report the patients were incompletely characterized as to the prevalence of cardiovascular abnormalities prior to randomization. The present report determines the relationship between prior cardiovascular damage and the effectiveness of treatment. The influences of age and blood pressure also are analyzed in more detail than in the original paper. The prerandomization blood pressures given in this and in the initial report[1] represent the average of the readings taken by the physician during the last two outpatient visits preceding randomization. Finally, additional data with respect to side effect and dose modifications are presented.

Influence of Age

The median ages were given in the initial report[1] as 49.2 years for the control group and 48.1 years for the treated series.

Additional data are presented in table 1. Fifty-one percent of the control and 55% of the treated group were less than 50 years of age. Approximately one fourth of the patients were in the 50–59-year age group. The 60 and above age group included 22.1% of the control and 20.5% of the treated patients, the oldest patient being 75 years of age.

The prerandomization blood pressures for the different age groups are shown in table 2. Systolic blood pressure was related directly to age, and averaged 154 mm Hg in the patients under 40 years of age and rose with age to 178 mm Hg in the 70–75-year age group. Mean diastolic blood pressures, however, were essentially the same at all ages. There were no significant differences in blood pressure in the control and treated patients.

Information on the duration of known hypertension indicated that 48% had recognized hypertension for 5 years or more, and 29% had hypertension for 9 years or more. The relatively high prevalence of hypertension of long duration may be explained in part by the age distribution and in part by the fact that the sample included only patients with "fixed" hypertension, namely those with diastolic blood pressures averaging 90 mm Hg or more from the fourth through the sixth day of hospitalization.

The incidence of morbid events during the study by age at randomization is listed in table 3. As would be expected, the incidence of major complications rose with age. In the control group, 15.2% of the patients under age 50 years developed morbid events following randomization as compared to 62.8% of the patients above age 59 years. In the treated patients, the percentage incidence of morbid events was 6.9 and 28.9%, respectively, in these two age groups. Treatment appeared to be effective in all age groups. The effectiveness of

Table 1

Age Distribution of Patients

Age (years)	Control		Treated		Total	
	No.	%	No.	%	No.	%
24–39	22	11.3	32	17.2	54	14.2
40–49	77	39.7	70	37.6	147	38.7
50–59	52	26.8	46	24.7	98	25.8
60–69	28	14.5	23	12.5	51	13.4
70–75	15	7.7	15	8.0	30	7.9
Total	194	100.0	186	100.0	380	100.0

Table 2

Relationship between Age and Blood Pressure prior to Randomization

Age (years)	Mean blood pressure (mm Hg)* Control group Systolic	Control group Diastolic	Treated group Systolic	Treated group Diastolic	Total Systolic	Total Diastolic
24–39	151.6	104.4	155.2	103.4	153.7	103.8
40–49	159.5	104.5	159.2	105.2	159.4	104.8
50–59	169.5	105.2	163.2	104.7	166.5	105.0
60–69	176.2	104.9	169.7	101.4	173.3	103.3
70–75	173.7	100.4	182.9	106.0	178.3	103.2
All ages	164.8	104.4	162.7	104.4	163.8	104.4

*Average of last two clinic visits prior to randomization.

Table 3

Incidence of Morbid Events with Respect to Age at Randomization

Age (years)	Control group No. rand	Control group With events No.	Control group With events %	Treated group No. rand	Treated group With events No.	Treated group With events %	Effectiveness of treatment* (%)
<50	99	15	15.2	102	7	6.9	55
50–59	52	14	26.9	46	4	8.7	68
60+	43	27	62.8	38	11	28.9	54
Total	194	56	28.9	186	22	11.8	59

*Difference between percent incidence of events in control and treated groups divided by percent incidence in control group.

Table 4

Incidence of Assessable Events by Age and Diagnostic Category

Diagnostic category	Age (years) <50 C	<50 T	50-59 C	50-59 T	60+ C	60+ T	Total events C	Total events T
Cerebrovascular accident	5	1	5	1	10	3	20	5
Congestive heart failure	1	0	1	0	9	0	11	0
Accelerated hypertension or renal damage	5	0	2	0	0	0	7	0
Coronary artery disease*	4	4	4	2	5	5	13	11
Atrial fibrillation	0	2	0	1	2	0	2	3
Dissecting aneurysm	0	0	1	0	1	0	2	0
Other†	0	0	1	0	0	3	1	3
Total morbid events	15	7	14	4	27	11	56	22
Diastolic > 124 mm Hg	15	0	3	0	2	0	20	0

Abbreviations: C = control group; T = treated group.

*Myocardial infarction or sudden death.

†Includes in treated group one patient terminated because of hypotensive reactions, one death from ruptured atherosclerotic aneurysm, and one patient with second-degree heart block. In control group includes one patient with left bundle-branch block.

treatment in preventing morbid events was estimated from the difference in the percentage incidence of major complications between control and treated patients divided by the percentage incidence in the control patients (table 3). Treatment was 55% effective in the

subsample below 50 years of age, 68% in the 50–59-year age group, and 54% in the patients aged 60 years and over.

The relationship between age and type of morbid event is shown in table 4. In the control group the most frequent complications in the oldest age group were cerebrovascular accidents and congestive heart failure. The latter was uncommon below age 60 years. However, increasing hypertension or progressive renal damage occurred predominantly in the control patients below age 50 years. Coronary artery disease occurred in all age groups but its percentage incidence was more common in the patients aged 60 years or over (tables 1, 4). Unlike the other categories, the complications of coronary artery disease did not appear to be affected by treatment.

Influence of Prior Cardiovascular Abnormalities

The prevalence of cardiovascular-renal abnormalities found prior to randomization is summarized in table 5. In grading the optic fundi, "hypertensive" and "sclerotic" changes were evaluated separately. Grade 1 hypertensive changes were defined as a probable decrease in arteriolar caliber with an A-V ratio of approximately 1:2, while grade 2 changes indicated a definite decrease in arteriolar caliber ranging from an A-V ratio less than 1:2 to threadlike arterioles. Because of the difficulty and variability in differentiating grade 1 from normal, only the grade 2 changes are reported. Such changes occurred in 31% of the control and 25% of the treated patients. Grade 2 sclerotic as opposed to hypertensive changes were defined as scattered prominent A-V nicks or asymmetric irregularity of arteriolar segments. Such changes were reported in 24% of patients.

Backgound charactistics were analyzed to determine the presence of cardiac, central nervous system (CNS), or renal abnormalities. All patients with severity grades[2] greater than zero with respect to any of these target organ systems were included with the following exceptions: headache, if this was the only CNS abnormality, and dyspnea on heavy effort if it was the only cardiac abnormality; optic fundi scores also were not included. Patients with dyspnea on ordinary activity, angina, left ventricular enlargement (LVE), cardiomegaly by X-ray, neurologic symptoms other than headache, or renal score greater than zero were included. On the basis of these criteria, 55% of the control group and 60% of the treated patients exhibited one or more abnormalities in the major target organ systems (table 5).

Ungerleider criteria[3] were used for determining cardiomegaly from the standard posterior-anterior X-ray of the chest. By these criteria, 22% of the control group and 28% of

Table 5

Prevalence of Cardiovascular-Renal Abnormalities prior to Randomization

Abnormality	Control group		Treated group		Total	
	No.	%	No.	%	No.	%
Optic fundi-grade 2 (hypertensive changes)*	60	31.0	46	24.8	106	27.9
Any cardiac, CNS, or renal abnormality*	107	55.2	112	60.2	219	57.6
Cardiomegaly (X-ray)*	42	21.7	53	28.5	95	25.0
LVE (ECG)*	32	16.5	30	16.1	62	16.3
Renal grade 1*	23	11.9	23	12.4	46	12.1
Renal grade 2*	4	2.1	4	2.1	8	2.1
Myocardial infarct	14	7.2	13	7.0	27	7.1
Congestive heart failure*	12	6.2	17	9.1	29	7.6
Cerebral thrombosis	10	5.2	9	4.8	19	5.0
Patients randomized	194	100.0	186	100.0	380	100.0

*Defined in text.

the treated patients were considered to exhibit cardiomegaly prior to randomization.

The electrocardiographic criteria for left ventricular enlargement (LVE) required that the patient exhibit both voltage changes (S in V_1 or V_2 plus R in V_5 or $V_6 > 35$ mm) and flat, biphasic, or negative T waves in leads I, aV_L, and V_5 or V_6. Sixteen percent of both the control and treated groups exhibited LVE by these criteria prior to randomization.

Renal damage was graded as follows. Grade 1 included any two of the following: specific gravity of 1.020 or less in all of three separate overnight urine collections, proteinuria of 1+ or more in any one of these specimens, and phenosulfonphthalein (PSP) excretion of less than 45% in a pooled 2-hour specimen. Grade 2 changes included any two of the following: specific gravity of 1.015 or less, proteinuria 1+ or more in all of three daily specimens, and PSP excretion of 30% or less. Grade 3 indicated all three of the above changes. Grade 4 denoted the presence of azotemia.

The frequency of grades 1 and 2 renal changes was the same in control and treated groups with 12% exhibiting grade 1 and 2% exhibiting grade 2 changes (table 5). None of the patients exhibited grade 3 changes. There were four patients in the control group and three in the treated series in whom the blood urea nitrogen was reported as being in the range of 25 to 32 mg/100 ml. However, the serum creatinine value was normal in four of these patients, and they did not develop morbid events following randomization. Of the remaining three patients, one died of a carcinoma of the urinary bladder, another developed congestive heart failure, while the third, who had chronic glomerulonephritis (GN) with serum creatinine of 2.4 mg/100 ml initially, was later removed from the trial because of elevated diastolic blood pressure.

Five patients, two in the control and three in the treated group, were diagnosed as having primary renal disease. Chronic glomerulonephritis was diagnosed in four and bilateral medullary sponge kidney in one. One of the two control patients with chronic GN was removed because of elevated diastolic blood pressure (see above) while the other developed a cerebral thrombosis. In the three actively treated patients with primary renal disease there were no morbid events.

Included in the study were some patients who had previous major events. Seven percent of the 380 patients, equally divided between control and treated groups, had sustained a myocardial infarction prior to randomization. Six percent of the control group and 9% of the treated patients had a past history of cardiac decompensation but were not in congestive heart failure at the time of randomization. Five percent of patients in both the control and treated groups had a clinical diagnosis of cerebral thrombosis. Patients with a history of other major complications of hypertension such as cerebral or subarachnoid hemorrhage, persistent congestive heart failure requiring continuous diuretics, accelerated phase of hypertension, or acute hypertensive encephalopathy were not admitted into the trial.

Cardiovascular-renal abnormalities were more frequent in the older patients (table 6). In those under 50 years of age, 46% presented with one or more abnormalities as opposed to 65% of the 50–59-year age group and 78% of the patients above age 59 years.

The presence of prior cardiovascular damage greatly increased the risk of developing morbid events following randomization (table 7). In the patients with either myocardial infarction, congestive heart failure, or cerebral thrombosis prior to randomization, subsequent major complications occurred in 53% of the control and 26% of the treated group during the postrandomization period. In those with evidence of cardiac, CNS, or renal damage but without a major complication preceding randomization, the incidence of subsequent morbid events was 33% in the control patients and 8% in the treated group. Effectiveness of treatment for the combined subsamples presenting with prerandomization abnormalities was 64% (table 7).

The incidence of morbid events was much less in the control series of patients presenting without abnormalities. In this subsample, 16% of the control patients developed a major

Table 6

Relationship between Age and Presence of Cardiac, CNS, or Renal Abnormality prior to Randomization

Age (years)	Control group			Treated group			Total		
	No. rand	With abnormality		No. rand	With abnormality		No. rand	With abnormality	
		No.	%		No.	%		No.	%
<40	22	9	40.9	32	13	40.6	54	22	40.7
40–49	77	29	37.7	70	41	58.6	147	70	47.6
50–59	52	34	65.4	46	30	65.2	98	64	65.3
60+	43	35	81.4	38	28	73.7	81	63	77.8
Total	194	107	55.2	186	112	60.2	380	219	57.6

Table 7

Incidence of Morbid Events with Respect to Prerandomization Cardiac, CNS, or Renal Abnormality

Status prerandomization	Control group			Treated group			Effectiveness of treatment (%)
	No. rand	With events		No. rand	With events		
		No.	%		No.	%	
With abnormality:							
Prior MI, CHF, CVA	34	18	53.0	38	10	26.4	50
All other	73	24	32.9	74	6	8.1	75
Subtotal	107	42	39.3	112	16	14.3	64
No abnormality	87	14	16.1	74	6	8.1	50
Total	194	56	28.9	186	22	11.8	59

complication as opposed to 8% of the treated. The difference is not statistically significant although the trend indicating 50% effectiveness of treatment is similar to that found in the group with preexisting abnormalities.

It should be emphasized that 20 control patients were removed from the trial prior to any morbid event because of elevations of diastolic pressures to more than 124 mm Hg which persisted for 3 weeks or longer.[1] Seven of the 20 patients had a prerandomization clinic diastolic blood pressure lower than 105 mm Hg. Fifteen of the 20 were less than 50 years of age; 10 of the 20 had no evidence of cardiac, CNS, or renal abnormality. Since at this level of diastolic blood pressure the risk of developing subsequent events without treatment is very high,[4] the removal of these patients prior to the development of a morbid event probably resulted in an underestimate of the effectiveness of treatment in all subgroups but especially in the subgroup under age 50 years and the group presenting without cardiac, CNS, or renal abnormalities.

Among the 27 fatalities occurring during the randomized trial, 17 deaths were associated with myocardial infarction or occurred suddenly; of these, 11 occurred in the control group and six in the treated patients. With respect to other risk factors in these 17 patients, six of the control and two of the treated patients had prerandomization serum cholesterol levels greater than 260 mg/100 ml. Two control patients and one treated patient exhibited fasting blood sugar levels above 110 mg/100 ml. There was no evidence of hypokalemia during the annual examinations in any of the patients who had sudden death.

Congestive heart failure occurred in 11 of the control patients. In five it represented a recurrence, while in six the initial attack occurred following randomization. Although 17 of the treated patients had a history of congestive heart failure prior to randomization, none developed recurrences during the postrandomization period.

Influences on Therapeutic Effectiveness

Because of the separate effects of level of diastolic blood pressure,[1] age, and prior cardiovascular abnormalities on the incidence of

Table 8

Attack Rates and Effectiveness of Treatment in Relation to Any One or Two Risk Factors at Entry

Risk factors at entry	Control group		Treated group		Effectiveness of treatment (%)
	No. rand	Attack rate*	No. rand	Attack rate*	
		By single risk factor			
Diastolic pressure:					
90–104 mm Hg	84	0.263	86	0.144	45
105–144 mm Hg	110	0.309	100	0.096	69
Age:					
<50 years	99	0.145	102	0.064	56
50+ years	95	0.439	84	0.184	58
CVR abnormalities:					
Without abnormality	87	0.161	74	0.081	50
With abnormality	107	0.393	112	0.143	64
		By two risk factors			
CVR abnormalities and diastolic B P:					
Without abnormality					
90–104 mm Hg	36	0.145	38	0.114	21
105–114 mm Hg	51	0.173	36	0.046	73
With abnormality					
90–104 mm Hg	48	0.352	48	0.168	52
105–114 mm Hg	59	0.426	64	0.124	71
CVR abnormalities and age:					
Without abnormality					
<50 years	61	0.098	48	0.040	59
50+ years	26	0.311	26	0.157	50
With abnormality					
<50 years	38	0.222	54	0.085	62
50+ years	69	0.487	58	0.196	60
Age and diastolic B P:					
<50 years					
90–104 mm Hg	43	0.121	46	0.088	27
105–114 mm Hg	56	0.164	56	0.043	74
50+ years					
90–104 mm Hg	41	0.413	40	0.208	50
105–114 mm Hg	54	0.459	44	0.163	64

*By regression data. See text.

Abbreviation: CVR = cardiovascular-renal abnormalities.

morbid events it seemed of interest to assess the influence of various combinations of these factors. Subdivision of the patient population into small subgroups increases the likelihood of large errors in observed rates due to random fluctuations. Therefore, rates were estimated by the use of multiple regression technics which, like curve fitting, smooth out some of the random fluctuations in the observed data.

The multiple regression technic likewise can provide improved estimates for the larger subgroups (all patients presenting with a given risk factor). Thus, the technic has been used to restate the attack rates for subgroups previously described, e.g., the younger group versus the older group. Such improved estimates are shown in the first section of table 8. Of course, the calculated "effectiveness of treatment" is modified to some degree.

With regard to combinations of risk factors the results indicate that the greatest benefit of treatment was achieved in the subgroups with diastolic blood pressure of 105–114 mm Hg

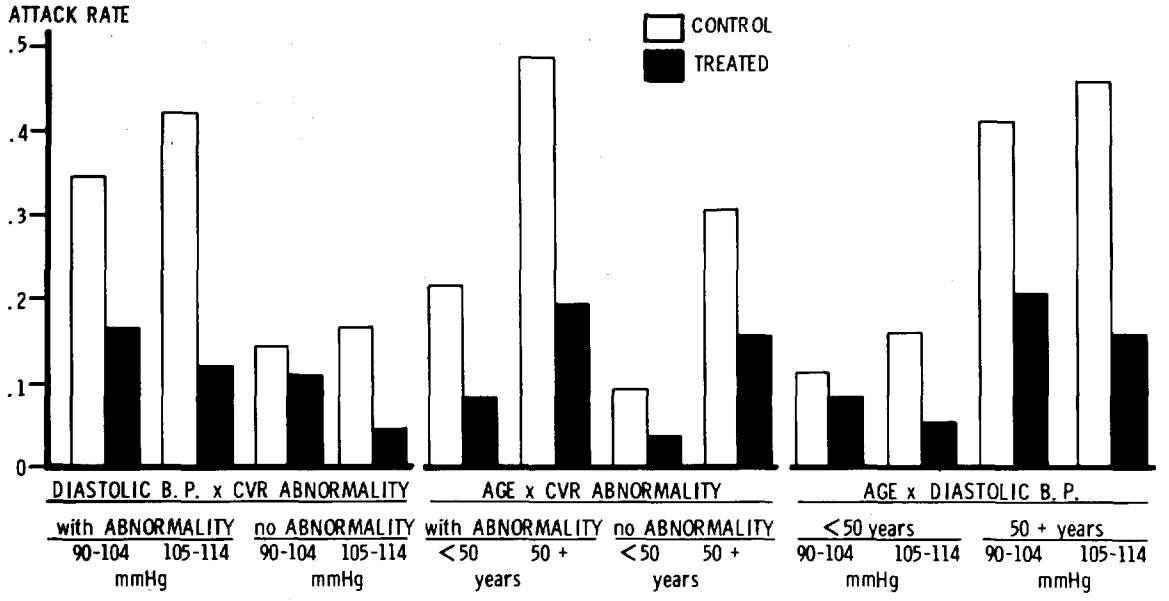

Figure 1

Attack rates computed by multiple regression data for control (clear columns) and treated (black columns) patients.

Table 9

Attack Rates and Effectiveness of Treatment in Relation to the Prevalence of Risk Factors at Entry

Risk factors at entry*	Control group		Treated group		Effectiveness of treatment (%)
	No. rand	Attack rate†	No. rand	Attack rate†	
None	24	0.066	22	0.069	—
Any one	68	0.171	66	0.087	49
Any two	62	0.363	64	0.138	62
All three	40	0.509	34	0.173	66

*Risk factors are (1) age over 50 years, (2) CVR abnormalities, and (3) diastolic blood pressure 105–114 mm Hg.

†By regression data.

regardless of evident cardiovascular-renal disease and irrespective of age (table 8, fig. 1). Treatment was least effective in two subgroups: those with initial diastolic blood pressure below 105 mm Hg and no cardiovascular, CNS, or renal abnormalities; and those below age 50 years with similar levels of blood pressure. These results, of course, may be considerably influenced by the relatively brief period of follow-up.

Table 9 indicates attack rates and effectiveness of treatment in relation to prevalence of the three risk factors at entry irrespective of the type of risk factor. Both attack rates and effectiveness of treatment are lowest when no risk factors are present and increase progressively with increasing prevalence of risk factors.

Side Effects

The initial report[1] indicated that two treated patients were removed from the trial because of presumed toxic reactions, one being anaphylactoid purpura, the other suspected, but unproven, lupus syndrome. In addition, there were 30 patients in whom the

suspected offending drug or its placebo was discontinued because of presumed drug-related side effects. Twelve of these patients developed mental depression, of whom seven were in the treated group and five in the control group. Ten patients developed peptic ulcer; six had been taking active drugs and four placebos. Two patients, one on active drugs the other on placebos, had a change in regimen because of impotence. The remaining six patients all were receiving active treatment. Their side effects included excessive sleepiness, severe nasal stuffiness, gout, seizures presumably caused by hypotension, and an abnormal glucose tolerance test.

Biochemical Side Effects

Hypokalemia. As indicated in table 10, the distribution of serum potassium levels prior to randomization was nearly identical in the control and treated patients with only 1% of the control and 2% of the treated patients exhibiting subnormal values. At the first annual examination, however, the percent distributions in the treated group shifted toward lower values of serum K while the control group remained essentially unchanged. At the end of 1 year, 2% of the control and 23% of the treated group exhibited subnormal values. However, only 1% of the treated patients exhibited a serum K level below 2.5 mEq/liter. A similar trend was found at the second annual examination, although there were no patients in the treated group who had a serum potassium level below 2.5 mEq/liter.

Of the patients completing two annual examinations, approximately half of the 23 treated patients who exhibited serum K levels under 3.5 mEq/liter at the first annual examination remained hypokalemic at the second annual examination. Five of the patients exhibiting subnormal serum K values at the first annual examination received potassium supplements. Three of these exhibited normal serum K values at the second annual examination, while two remained mildly hypokalemic.

Serum Uric Acid. At the initial examination, 13% of the control group and 11% of the treated patients exhibited uric acid levels of 8.0 mg/100 ml or higher (table 11). At the first annual examination patients with elevations of 8.0 mg/100 ml or higher accounted for 16% in the control and 30% in the treated series; at the second annual examination the percentages were 19 in the control and 25 in the treated. In the 40 treated patients exhibiting hyperuricemia after 1 year, 18 had uric acid levels remaining at 8.0 mg/100 ml or higher at the second annual examination. Five of the patients exhibiting uric acid elevations at the first annual examination were placed on either allopurinol or probenecid; the uric acid remained elevated in three and fell below 8.0 mg/100 ml in two at the second annual examination. As indicated in the previous report,[1] two actively treated patients experienced their first attack of gout during the postrandomization period.

Fasting Blood Sugar. The data with regard to fasting blood sugar (FBS) are incomplete due to the fact that the 2-hour postprandial blood sugar was substituted for FBS at a few hospitals during the first 3 years of the trial.

Table 10

Percent Distribution of Serum Potassium Levels on Initial and First and Second Annual Examinations

Serum K (mEq/liter)	Initial (%)		First annual (%)		Second annual (%)	
	C	T	C	T	C	T
2.0–2.4	0	0	0	1	1	0
2.5–3.4	1	2	2	22	2	20
3.5–4.4	49	51	52	63	59	58
4.5+	50	47	46	14	38	22
Total patients	194	186	168	167	137	137

Abbreviations: C = control group; T = treated group.

Table 11

Percent Distribution of Serum Uric Acid Levels on the Initial and First and Second Annual Examinations

Serum uric acid (mg/100 ml)	Initial (%)		First annual (%)		Second annual (%)	
	C	T	C	T	C	T
<6.0	43	55	41	23	37	31
6.0 – 7.9	44	34	43	47	44	43
8.0 – 9.9	11	10	15	25	16	16
10.0 – 11.9	2	1	1	3	2	7
>11.9	0	0	0	2	1	2
Total patients	194	186	168	167	137	137

Abbreviations: C = control group; T = treated group.

The prevalence of FBS values of 110 mg/100 ml or higher was essentially the same in the control and treated groups prior to randomization (table 12). One year after randomization, however, the prevalence was 20.8% in the treated series as compared to 15.6% in the control, and 2 years after randomization it was 30.0% in the treated and 17.0% in the control patients. FBS levels of 120 mg/100 ml were found in 7.0% of the treated patients prior to randomization, 12.5% at the first annual, and 14.6% at the second annual examination.

Because of the difference in total patients available for examination at the end of the first and second year of follow-up (table 12), the data also were analyzed using as denominators only the patients who completed both the first and second annual examinations. The results still indicated a greater percentage of patients with elevated FBS in the treated as compared to the control group of patients.

There was no significant correlation between reduction in serum K and the increase in FBS in the treated group of patients. After 1 year of treatment mean serum K was 3.91 SD 0.57 mEq/liter in 119 treated patients with FBS levels below 110 mg/100 ml and 3.89 SD 0.57 mEq/liter in 40 treated patients with FBS levels of 110 mg/100 ml or higher. After 2 years, the serum K levels were 4.04 SD 0.58 and 3.98 SD 0.91 mEq/liter, respectively, in the two groups.

Changes in Doses of Protocol Drugs

At the time of randomization a combination of hydrochlorothiazide 50 mg and reserpine 0.1 mg twice daily plus hydralazine 25 mg three times daily[5] were administered to all patients in the treated group.* Obviously, this therapeutic regimen will result in a higher incidence of side effects than the usual method of initiating treatment with a single antihypertensive agent. Therefore, provision was made

*The special medications used in this study were prepared by Dr. William E. Wagner of Ciba Pharmaceutical Co., Summit, New Jersey.

Table 12

Percent Distribution of Fasting Blood Sugar Levels on the Initial and First and Second Annual Examinations

Fasting blood sugar (mg/100 ml)	Initial (%)		First annual (%)		Second annual (%)	
	C	T	C	T	C	T
<110	85.2	85.4	84.4	79.2	83.0	70.0
110–119	6.5	7.6	9.5	8.3	8.1	15.4
120+	8.3	7.0	6.1	12.5	8.9	14.6
Total patients	169	172	148	144	123	123

Abbreviations: C = control group; T = treated group.

Table 13

Dose Changes in a Representative Subsample of 56 Control and 68 Treated Patients

Dose change	No. of patients		Reasons for change (treated group only)			
	Control	Treated	Hypotension*	Angina	Headache	Other
Hydralazine reduced	3	6	4	0	1	1
Hydralazine omitted	0	8	5	1	2	0
Thiaserp† reduced	0	6	6	0	0	0
Both reduced	0	5	4	1	0	0
Thiaserp reduced and hydralazine omitted	1	8	7	1	0	0
Special Thiaserp‡	1	1	0	0	0	1
Other	4	2	2	0	0	0
Total	9§	36	28	3	3	2
% of sample	16	53	41	4.5	4.5	3

*Diastolic below 90 mm Hg with weakness, lethargy, faintness, etc.

†Combination tablet containing 50 mg hydrochlorothiazide and 0.1 mg reserpine. Standard dose 1 tablet twice daily.

‡Thiaserp without reserpine.

§Reasons for changing doses of placebos were as follows: angina in three patients, headache in one, nasal stuffiness in one, skin rash in one, and multiple complaints in two.

for reducing doses or for discontinuing one of the three drugs in the presence of hypotensive symptoms or other side effects.

A sample of 124 patients was taken of the 380 randomized into the trial. Their case records were examined for modifications in doses and for the reason for the changes. The sample was chosen in a way which would contribute proportionate numbers from each of the participating clinics and would span the time period during which the patients were entered into the trial.

Doses were modified in nine (16%) of the control sample and in 36 (53%) of the treated sample (table 13). In the placebo group the reasons for changing doses included the following side effects: headache, nasal stuffiness, angina, skin rash, and multiple complaints. In the treated group 28 of the 36 patients whose regimens were modified had their doses reduced mainly because of hypotensive symptoms of weakness, lethargy, or faintness associated with a fall of diastolic blood pressure to levels usually well below 90 mm Hg. These symptoms abated following appropriate reductions in doses. Side effects other than hypotensive symptoms leading to changes in doses included angina in three patients, headache in three, nervousness in one, and nasal stuffiness in one patient. Thus, the incidence of side effects *other than hypotension* leading to changes in doses was not significantly different in the control and treated groups. Hypotensive symptoms probably would have been far less if treatment had been initiated with a single antihypertensive agent.

Incidence of Subjective Side Effects

Subjective side effects in the same subsample of 124 patients were evaluated from a physician's interview checklist contained on the clinic visit report forms. The reports for the last two visits during the prerandomization trial period and all postrandomization visits were reviewed.

Probably because of different value judgments used by the various clinic physicians there was considerable variation from one hospital to another regarding the frequency with which specific complaints were reported. Since the same physician always saw a particular patient it seemed valid to compare the postrandomization against the prerandomization period for each patient. In any particular patient only those side effects were counted which were complained of solely during the postrandomization period and which were not noted prior to randomization.

The results indicate a surprising number of patients complaining of specific side effects in the group of patients randomized on placebos. For example, of 52 patients in the control group who did not complain of nightmares prior to randomization, six reported this "side effect" at some time following randomization (table 14). For the specific complaints of nightmares, arthritis, angina, and headache, the incidence actually was greater in the control group of patients than in the treated group. The incidence was nearly equal for both control and treated groups for the side effects of depression, skin rash, impotence, and "other complaints." A possible explanation for the high incidence of "side effects" is that the physician may have paid more attention to the side effects interview following randomization.

The only side effects occurring with greater frequency in the treated group of patients were lethargy or weakness, nasal stuffiness, ulcer symptoms, and first appearance of any complaint. The latter refers to the patients who had no complaints of any kind prior to randomization but who reported one or more side effects following randomization.

It also seemed important to examine the incidence of side effects after appropriate maintainence doses of the antihypertensive drugs had been obtained. Therefore, data relating to the reporting of specific side effects omitting the first two postrandomization visits (third and subsequent visits only) also are presented in table 14. For these latter visits the reporting of complaints of ulcer symptoms, lethargy or weakness, and nasal stuffiness were insignificantly different in the control and treated groups of patients. It is interesting that during these visits the reporting of angina and headache was considerably higher for the control as compared to the treated group of patients.

Discussion

The incidence of morbid events in the present study was higher than would be expected in the general population of hypertensive patients. The reasons for this probably include the following: (1) patients with hypertension on admission but whose diastolic blood pressure averaged below 90 mm Hg during the fourth through sixth day of hospitalization were excluded; (2) more than half of the patients presented with cardiovascular or renal abnormalities; (3) in almost 30% of the patients hypertension was known to be present for 10 years or longer; and (4) while

Table 14

Incidence of Specific Side Effects among a Subsample of 56 Control and 68 Treated Patients

Side effect	Control group					Treated group				
	Without prev complaint* (no.)	With complaint postrand				Without prev complaint* (no.)	With complaint postrand			
		Any visit		After 2nd visit			Any visit		After 2nd visit	
		No.	%	No.	%		No.	%	No.	%
Nightmares	52	6	12	4	8	65	4	6	2	3
Depression	53	5	9	5	9	67	6	9	5	7
Skin rash	55	5	9	4	7	64	5	8	5	8
Arthritis	50	19	38	16	32	63	17	27	15	24
Impotence	46	13	28	10	22	62	18	29	13	21
Angina	49	12	24	9	18	64	8	13	6	9
Headache	38	13	34	8	21	52	13	25	4	8
Ulcer symptoms	55	5	9	5	9	68	8	12	6	9
Lethargy or weakness	46	12	26	8	17	64	25	39	13	20
Nasal stuffiness	48	14	29	10	21	63	22	35	10	16
Other complaints	47	20	43	16	34	58	25	43	18	31
Any complaint†	24	16	67	15	63	40	33	82	31	78

*Patients who did not have the specific complaint prior to randomization.

†Patients without any of the above complaints prior to randomization, and those who subsequently developed some complaint.

only one fifth of the patients were above 60 years of age such patients contributed half of the morbid events.

The incidence of morbid events in the control group was greater in patients with initial levels of diastolic blood pressure averaging 105–114 mm Hg than in those with 90–104 mm Hg at entry. The effectiveness of treatment was much greater for those with the higher initial blood pressure levels. In the present communication it is shown that preexisting cardiovascular disease markedly increases the risk of developing events in the control group and that the effectiveness of treatment over the limited period of observation was greater in those with such evidence of prior disease.

Termination of the trial was necessitated by the clear-cut evidence of benefit in the treated group as compared to the controls. Since the patients without evidence of cardiovascular disease were at reduced risk, follow-up was of too brief duration for the occurrence of many events or to obtain a statistically significant difference between control and treated groups in this subsample. However, the observed 50% effectiveness of treatment in the "no abnormality" group, which was not substantially different from the 64% effectiveness found in the group with abnormalities, is consistent with a protective effect of treatment.

The results of the present trial justify more intensive efforts to identify and maintain under adequate treatment patients with any signs of cardiovascular damage or with diastolic blood pressure averaging in excess of 104 mm Hg. Evidence from surveys carried out in representative population groups[6, 7] indicate that many of these patients are either unaware of their hypertension or are not receiving adequate treatment.

Additional evidence will be required, however, to determine whether the benefits of treatment outweigh its disadvantages in lower risk patients, such as in those with mild hypertension and no evidence of vascular disease, particularly in women, and in patients with labile hypertension. Toxic reactions may occur with any of the presently available antihypertensive agents, and side effect, particularly biochemical changes associated with thiazides and related diuretics, are relatively common. Modifications of doses often are required because of other disturbing side effects. While the risk associated with these various side effects appears small, it must be considered in relation to the benefit to be expected in treating patients whose risk of developing complications due to hypertension also is relatively low. If patients are not treated, however, they should be followed periodically to determine whether the hypertension progresses to a more severe stage. Such follow-up appears to be particularly important in younger patients. In the present study, 15 of the 20 control patients whose diastolic blood pressures became severely elevated were below 50 years of age; seven had an initial diastolic blood pressure below 105 mm Hg.

In the present sample of patients, antihypertensive treatment appeared to be effective in reducing the complications associated with hypertension except for myocardial infarction and sudden death. This result is not necessarily inconsistent with the statistical evidence that elevated blood pressure is one of the "risk factors" associated with an increased incidence of coronary heart disease. It is possible that a larger sample size or a longer period of follow-up might have revealed differences not apparent in the present study. Also, a greater degree of protection might have been afforded if treatment had been instituted at an earlier stage of hypertension. Therapeutic trials are needed in a different population of hypertensive patients in order to resolve this question.

Acknowledgments

We wish to thank Drs. Jacques Genest, Ray W. Gifford, Jr., Walter M. Kirkendall, Louis Lasagna, David W. Richardson, and Robert W. Wilkins for valuable consultation and advice.

References

1. Veterans Administration Cooperative Study Group on Antihypertensive Agents: Effects of treatment on morbidity in hypertension. II: Results in patients with diastolic blood

pressure averaging 90 through 114 mm Hg. JAMA **213:** 1143, 1970

2. VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP ON ANTIHYPERTENSIVE AGENTS: A double-blind control study of antihypertensive agents. I: Comparative effectiveness of reserpine, reserpine and hydralazine, and three ganglionic blocking agents, chlorisondamine, mecamylamine and pentolinium tartrate. Arch Intern Med (Chicago) **106:** 81, 1960
3. UNGERLEIDER HE, GUBNER R: Evaluation of heart size measurements. Amer Heart J **24:** 494, 1942
4. VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP ON ANTIHYPERTENSIVE AGENTS: Effects of treatment on morbidity: Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. JAMA **202:** 1028, 1967
5. VETERANS ADMINISTRATION COOPERATIVE STUDY GROUP ON ANTIHYPERTENSIVE AGENTS: A double-blind control study on antihypertensive agents. III: Chlorothiazide alone and in combination with other agents. Arch Intern Med (Chicago) **110:** 230, 1962
6. WILBER JA: Detection and control of hypertensive disease in Georgia, U.S.A. *In* The Epidemiology of Hypertension, edited by Stamler J, Stamler R, Pullman TN. New York, Grune & Stratton, 1967, p 439
7. STAMLER J, ET AL.: Detection of susceptibility to coronary disease. Bull NY Acad Med **45:** 1306, 1969